REMARKS

Previously, Claims 22-36 and 39-58 were pending. In the instant amendment, Claims 25, 26, 42 and 43 have been canceled. Claims 22 and 39 have been amended. After entry of the instant amendment, Claims 22-24, 27-36, 39-41 and 44-58 will be pending and under consideration.

Applicants' attorneys thank Examiner Falk for the telephone interview on October 4, 2004, during which the written description rejection of Claim 39 and the enablement rejection were discussed.

I. AMENDMENTS TO THE CLAIMS

Claims 25, 26, 42 and 43 have been canceled, without prejudice to Applicants' rights to pursue the subject matter of the canceled claims in related applications.

Support for the amendment to Claim 22 is found in the specification, for example, at page 5, lines 18-21; page 10, lines 10-16; page 12, line 8, to page 13, line 20.

Support for the amendment to Claim 39 is found in the specification, for example, at page 26, lines 12-20, and page 27, lines 12-17.

No new matter is introduced with these amendments. Applicants respectfully submit that the amendments are fully supported by the specification and claims as originally filed, and request entry thereof.

No amendment fee is believed to be due.

II. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION REQUIREMENT

Claims 22-36 and 39-58 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The rejection of Claims 25, 26, 42 and 43 is moot in view of the cancellation of these claims.

With respect to Claims 22-24, 27-36 and 54-58, that are directed towards nucleic acid molecules, the Patent Office alleges that the specification does not describe a representative number of nucleic acids encoding the genus of biofilament polypeptides as recited in the claim. Without acquiescing to the propriety of the rejection, Applicants respectfully submit that the rejection is obviated in view of the amendment to Claim 22, from which the other claims depend. In particular, the Patent Office acknowledges that the particular biofilament polypeptides from the two spider species recited in Claim 22 "permit construction of a nucleic acid construct as claimed." *See* Office Action, page 3. Applicants respectfully

submit that the written description requirement is met with respect to Claims 22-24, 27-36 and 54-58, and respectfully request that the rejection of Claims 22-24, 27-36 and 54-58 under 35 U.S.C. § 112, first paragraph, be withdrawn.

With respect to Claim 39 that is directed towards a transgenic female ruminant, the Patent Office alleges that the claim continues to encompass a female ruminant produced by *in vivo* somatic cell gene transfer whereby nucleic acid is delivered to somatic cells, but germ cells of a host. Claims 40 and 44-53 depend from Claim 39 and are included in this rejection. Without acquiescing to the propriety of the rejection, Applicants respectfully submit that the rejection is obviated in view of the amendment to Claim 39, that recites, in relevant portions, "a transgenic female ruminant comprising *germline and somatic cells* that comprise the nucleic acid molecule of claim 22 . . . ." Applicants respectfully submit that the written description requirement is met with respect to Claims 39, 40 and 44-53.

For the reasons discussed above, Applicants respectfully request that the rejection of Claims 22-36 and 39-58 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT REQUIREMENT

Claims 22-36, 39, 40, and 42-58 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The rejection of Claims 25, 26, 42 and 43 are moot in view of the cancellation of these claims. Applicants respectfully traverse the rejection of Claims 22-24, 27-36, 39, 40, and 44-58, since the specification, in conjunction with the state of art at the time the application was filed, provides a reasonable amount of guidance and direction for one of skill in the art to make the claimed nucleic acid molecule or transgenic ruminant, as well as to perform the recited methods. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art.").

The Declaration of Dr. Karatzas, filed April 18, 2002, provides evidence that the biofilament polypeptides, under control of a regulatory sequence, *can and do express* in milk-producing cells of a ruminant and that such polypeptides are secreted into the milk of the transgenic ruminant. In paragraphs 4a through 4c of the declaration, Dr. Karatzas explains that transgenic goats comprising nucleic acid encoding the ADF-3, MaSpI,[1] or MaSpII[2] biofilament polypeptides under control of the WAP promoter expressed biofilament

[1] Alternatively referred to as NcDS-1 in the instant specification.
[2] Alternatively referred to as NcDS-2 in the instant specification.

polypeptide in their milk. In paragraph 4c, Dr. Karatzas states that "some [goats] made more than 1 gram of MaSpII protein per liter of milk." Thus, the Patent Office is factually incorrect to assert that the nucleic acids recited in Claims 22-24, 27-36 and 54-58, the transgenic female recited in Claim 39 or the methods described in Claims 40 and 44-53 do not work for lack of expression, since the biofilament polypeptides recited in amended Claim 22 clearly can be expressed in milk.

Moreover, Applicants respectfully submit that the amounts of biofilament polypeptide expressed and secreted into the milk of the transgenic ruminants, including those ruminants generated from pronuclear microinjection (or transgenic ruminants that are the progeny of those generated from pronuclear microinjection), are sufficient to permit the isolation of the expressed and secreted biofilament polypeptides. The Declaration of Dr. Karatzas, filed April 18, 2002, for example, indicates that the two different biofilament polypeptides, ADF-3 and MaSpI, expressed in milk of transgenic animals were identified in the milk by Western blot and molecular weight measurement, which given that these techniques require the target protein to be isolated from other non-target protein, suggests that, in fact, ADF-3 and MaSpI are expressed in quantities sufficient to permit their isolation. *See* paragraphs 4a and 4b.

For the reasons discussed above, Applicants respectfully submit that Claims 22-24, 27-36, 39, 40, and 44-58 are enabled. Accordingly, Applicants respectfully request that the rejection of Claims 22-36, 39, 40, and 42-58 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 22-36 and 41-58 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Huynh *et al.* (1991) *Experimental Cell Research* 197:191-199, U.S. Patent No. 5,227,301 (Turner *et al.*, 1993), Fahnestock & Irwin (1997) *Appl. Micobiol. Biotechnol.* 47:23-32 and Ebert *et al.* (1994) *Bio/Technology* 12: 699-702. The rejection is moot with respect to Claims 25, 26, 42 and 43 in view of the cancellation of these claims. Applicants respectfully traverse the rejection of Claims 22-24, 27-36, 41 and 44-58.

To reject a claim under 35 U.S.C. § 103(a), the Patent Office bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1993). Three basic criteria must be met to establish a *prima facie* case of obviousness. First, the prior art must teach or suggest all the claim limitations. *In re Wilson*, 165 U.S.P.Q. 494, 496 (CCPA 1970). Second, art cited by the Patent Office must provide "motivation, suggestion, or teaching of the desirability of making

the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). Third, the cited references must provide a reasonable expectation of successfully achieving the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicants respectfully submit that *prima facie* obviousness has not been established since the Patent Office has not provided a suggestion, teaching or motivation in the cited references or in the art to modify the cited references. "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight" long proscribed by Federal Circuit precedent. *See, e.g., In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

Instant Claim 22 recites a nucleic acid molecule comprising a nucleotide sequence encoding a polypeptide and a regulatory sequence that directs expression of said polypeptide in milk-producing cells of a ruminant, wherein said regulatory sequence is operably linked to said nucleotide sequence, wherein said polypeptide comprises a biofilament polypeptide and a leader sequence that enables secretion of said biofilament polypeptide by said milk-producing cells into milk of the ruminant, and wherein said biofilament polypeptide comprises a plurality of repeat motifs as present in dragline silk produced by *Nephila clavipes* or *Araneus diadematus*. Claims 23, 24, 27-36 and 54-58, directed towards nucleic acid molecules depend from base Claim 22. Instant Claim 41 recites a method for producing a biofilament polypeptide, comprising culturing a mammary epithelial cell comprising the nucleic acid molecule of claim 22 under conditions in which said biofilament polypeptide is expressed and secreted into a culture medium of said culturing mammary epithelial cell and isolating said biofilament polypeptide from said culture medium. Claims 44-53 depend from Claim 41.

Huynh *et al.* and Turner *et al.* each disclose immortalized bovine mammary epithelial cell line referred to as MAC-T cells. The authors of these papers teach that MAC-T cells are useful for studying bovine lactation (Huynh *et al.* at 195; Turner *et al.* at col. 7, line 31, to col. 9, line 9). Neither reference, taken alone or combination, teaches or suggests a nucleic acid molecule comprising a biofilament polypeptide and a leader sequence that enables secretion of said biofilament polypeptide by said milk-producing cells into milk of the ruminant, and wherein said biofilament polypeptide comprises a plurality of repeat motifs as present in dragline silk produced by *Nephila clavipes* or *Araneus diadematus*, or methods of using the nucleic acid molecule to produce a biofilament polypeptide. The Patent Offices notes that in column 10 of Turner *et al.*, it is pointed out that "[e]ukaryotic fermentation is a

viable means of overcoming the considerable problems associated with prokaryotic expression of *mammalian* proteins." (Emphasis added). Nonetheless, Turner *et al.* does not teach or suggest nucleic acids encoding *non-mammalian* proteins, let alone spider silk biofilament polypeptides. Turner *et al.* also fails to teach or suggest expressing such polypeptides in the milk of a ruminant.

Fahnestock & Irwin describe the expression of spidroins 1 and 2 from *Nephila clavipes* in *E. coli*. Nowhere does Fahnestock & Irwin teach or suggest a nucleic acid molecule encoding spider silk polypeptides and a leader sequence that enables secretion of the biofilament polypeptide by milk-producing cells into milk of a ruminant, or a method of using the nucleic acid molecule to produce a biofilament polypeptide. The Patent Office states that Fahnestock & Irwin provides evidence that spider silk proteins have desirable properties and that skilled artisans are interested in producing these proteins in large quantities. This is an accurate statement of the problem facing the art, and one to which the instant application provides a solution. Applicants respectfully submit, however, that Patent Office has not met the legal requirement to provide a motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. Indeed, Fahnestock & Irwin do not teach or suggest using alternative expression systems, but only provide ideas on how to express spider silk proteins in *E. coli*.

The Patent Office notes that Fahnestock & Irwin state that spidroin 1 and 2 are poorly adapted to expression in *E. coli*. It is factually incorrect to characterize Fahnestock & Irwin as stating that the problems of expressing spider silk proteins in *E coli* as a result of that prokaryotic expression system. In Fahnestock & Irwin the problems associated with expressing the spider genes are described as being (1) a result of the DNA repetiveness (page 30, left col.) and (2) size heterogeneity in the expressed product due to abortive synthesis (page 30, right col). Fahnestock & Irwin, in fact, suggest using only codons favored by *E. coli*, and explain that using synthetic genes, as opposed to natural spider silk genes, "may be essential to allow alleviation of these difficulties...." *See* pages 30-31. Thus, nowhere does Fahnestock & Irwin provide a suggestion, motivation or teaching to combine its disclosure with that of Huynh *et al.* or Turner *et al.* Applicants respectfully submit that Fahnestock & Irwin teach away from using a nucleic acid molecule comprising a spider silk polypeptide with a leader sequence for expression in milk, since the solutions Fahnestock & Irwin provide are for expressing spider genes in *E. coli*.

Ebert *et al.* teach the production of human tissue plasminogen activator ("hTPA") in milk of transgenic goats. As with the references of Huynh *et al.*, Turner *et al.* and

Fahnestock & Irwin, nowhere in Ebert *et al.* do the authors teach or suggest a nucleic acid molecule encoding a spider silk biofilament polypeptide linked to a signal peptide for expression into milk, or methods of producing a biofilament polypeptide using such a nucleic acid. Moreover, given the differences between hTPA, a mammalian enzyme, and spider silk biofilament polypeptides, which are non-mammalian structural polypeptides, the expression of hTPA in goat milk described in Ebert *et al.* fails to suggest anything about the expression of biofilament polypeptides in milk.

In lieu of finding any suggestion, motivation or teaching in any of the cited references for their combination, the Patent Office contends that "given the problems revealed in attempting to express synthetic spider dragline silk polypeptides in *E. coli*, one of skill in the art would have realized that a eukaryotic expression system would be more compatible for expression of eukaryotic genes." But this is contradictory to Fahnestock & Irwin, for example, who discuss means of optimizing expression in an *E coli* expression system. Even assuming *arguendo* that one of skill would look for an eukaryotic expression system, there are numerous and diverse expression systems from yeast, plant and animal cell origins are available. Combining Huynh *et al.*, Turner *et al.*, Fahnestock & Irwin, and Ebert *et al.* without evidence of a suggestion, teaching, or motivation to do so takes Applicants' disclosure as a blueprint for piecing together the prior art to defeat patentability which is impermissible. *See, e.g., In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Applicants respectfully submit that Claims 22-36 and 41-58 are non-obviousness in view of the art cited by the Patent Office. Accordingly, Applicants respectfully request that the rejection of Claims 22-36 and 41-58 under 35 U.S.C. § 103(a) be withdrawn.

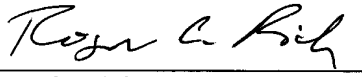
CONCLUSION

In light of the above amendments and remarks, Applicants respectfully request that the Patent Office reconsider this application with a view towards allowance.

No fee other than that for an extension of time are believed to be due. However, the Commissioner is hereby authorized to charge any required fee(s) to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: November 3, 2004



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